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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,356	11/21/2000	Shimpei Ushio	USHIO-2	8174

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/716,356	USHIO ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cov r she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9 and 18-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2 and 4-9* is/are allowed.

6)☒ Claim(s) *18-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Currently, claims 1, 2, 4-9, and 18-52 are pending and under consideration in this application. Claims 1,2, and 4-9 were indicated to be allowable, and claims 18 and 20-52 were rejected in the prior action. Claim 19 was objected to as depending from a rejected claim.

2. In the Response, filed November 13, 2003, amended claims 18, 19, and 21.

3. Because this action raises new issues not raised in the prior action, the rejection is being made Non-Final.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. **(New Rejection- Necessitated by Amendment)** Claims 18-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims have been amended to read on a pharmaceutical composition comprising SEQ ID NO: 6, or a fragment or homologue thereof, wherein the composition is administered in combination with or without a biologically active compound. Dependant claims further identify the biologically active compounds. However, it is unclear from the claims whether these biologically active

compounds are included in the claimed pharmaceutical compositions, or are merely administered at the same time or in the same therapy as the claimed composition.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **(New Rejection)** Claims 18, 20-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read, in relevant part, on pharmaceutical compositions comprising fragments of the interferon-γ inducing protein of SEQ ID NO: 6. It is noted that, unlike in claims 1 and 19, claim 18 and its dependant claims do not require that the fragments of the polypeptide have the biological activity of the polypeptide of SEQ ID NO: 6. Because the claim does not require that the polypeptide have any biological activity, the Applicant is not enabled for pharmaceutical compositions comprising such fragments. It is suggested that the Applicant amend claim 18 such that it reads on pharmaceutical compositions comprising - - an interferon-γ inducing polypeptide selected from the group consisting of a) a polypeptide of SEQ ID NO: 6 obtainable from humans, where amino acid residue 73 of SEQ ID NO: 6, as represented by Xaa, is Ile or Thr; b) a contiguous fragment thereof; or c) a homologous

polypeptide thereof...- - Such language would limit the fragments to those indicated in claim 1, and would overcome the rejection.

8. **(New Rejection- Necessitated by Amendment)** Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection. This claim has been amended from reading on the pharmaceutical compositions of claim 18 comprising a biologically active agent selected from a specific group of compounds to a biologically active agent selected from the group consisting of antitumor agents, antiviral agents, antiseptics, immunotherapeutic agents, platelet-increasing agents, and leukocyte-increasing agents. The Applicant has therefore amended claim 21 to read on compositions comprising genera of compositions for which there is no written description in the originally filed application. It is noted that the agent identified in this claim are listed on page 23 of the application. However, that section of the application is describing the functions and uses of the polypeptide of SEQ ID NO: 6, and is not identifying the biologically active agents that may be used with the polypeptide. Thus, there does not appear to be support for the newly added limitations of claim 21.

9. **(Prior Rejection- Maintained)** Claims 18, 20, and 21-52 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a

composition comprising SEQ ID NO: 6, or for derivatives thereof varying from SEQ ID NO: 6 by one amino acid residue, does not reasonably provide enablement for a composition comprising any homologue of the sequence. The claims read on compositions comprising the polypeptides of SEQ ID NO: 6, or homologous sequences comprising one or more (at least one) substitutions or deletions within the sequence of SEQ ID NO: 6.

The Applicant's arguments regarding the teachings of the WO 98/10072 are noted. The Applicant further traverses the rejection because, although the specification discloses only two homologous sequences, one of ordinary skill in the art could have easily obtained other homologous sequences. (It is noted that, as per the Applicant's argument with reference to the anticipation rejection over Okamura et al., the protein of SEQ ID NO: 4, although relevant to the enablement of homologues, is not a homologue covered by the present claims.) However, with respect to the homologous sequences disclosed by the Applicant, there has been no showing that the murine IGIF of SEQ ID NO: 4 would be capable of inducing interferon-gamma production in human cells as required by the claims. Further, as was previously indicated, the Applicant has provided little guidance as to what residues within SEQ ID NO: 6 may be substituted such that the biological activity of the protein is maintained. While the Applicant has provided one homologue of SEQ ID NO: 6, the Applicant has not, as indicated in the prior actions, what regions of the polypeptides are required for the interferon-γ inducing activity. The Applicant's alignment of SEQ ID NO: 4 and 6 (along with the IL-18/IGIF rat sequences) are noted. However, these alignments demonstrate that there are numerous areas of homology among the polypeptides throughout their length. Thus, these alignments demonstrate that one of ordinary skill in the art would not be able to easily determine which residues are necessary for the

indicated activity because there are no areas among these sequences that appear to be more closely related than others. From these teachings, one of ordinary skill in the art would not be able to associate any particular region or residues of the polypeptide with the interferon-γ activity.

Thus, the Applicant has provided little guidance as to the residues required to maintain the protein activity. However, as indicated in the prior actions, the claims read broadly on any homologue with any number of substitutions. Further, as indicated by the Bowie reference (cited in the action mailed on October 22, 2002, the effect of protein modification is unpredictable without teachings by which those in the art can identify the residues that are associated with the protein's function. Applicant's citation of the Watson reference is noted, however it is not found convincing. For example, the reference teaches on pages 224 and 229, respectively, that "*many* of the amino acids in proteins are not essential, and when they are replaced with somewhat similar amino acids, the proteins often *retain* full activity," and that it "is also *sometimes* possible to obtain functional genes by producing recombinants containing three closely spaced insertions or deletions." Thus, the teachings of this reference do not conflict with the teachings of Bowie. Rather, Bowie provides similar teachings, but also indicates that the effects of a particular substitution or change to a sequence is not generally predictable. Thus, while the art indicates that making changes to protein sequences is possible, it also indicates that, without teachings regarding the relationship of the residues to be mutated and the protein's function, those in the art cannot predictably create or identify homologues that retain the protein activity.

Furthermore, unlike claim 1 and its dependant claims, which allow for only a single mutation, the rejected claims allow for at least one mutation. Thus, these claims have a broader

scope, and include embodiments where any number of amino residues have been altered. Thus, if the effect of a single mutation is unpredictable, the mutation of multiple residues is even more so. Further, it is also known in the art that the effects of multiple mutations to a protein sequence is cumulative. See, Well, Biochem 29: 8509-8517. In addition to teaching that the effects of multiple mutations is additive, the reference also teaches that in certain cases such mutations may have more or less effect than simple additivity. Page 8509, left column. From these teachings it becomes further clear that the art of protein modification is complex in addition to being wrought with unpredictability.

It is further noted that the claims do not merely require that the homologues have the ability to induce interferon-γ production, but that they must be able to do so in *human* immunocompetent cells. The Applicant has not demonstrated that any homologue of Il-18 would be capable of inducing such production in human cells. The Applicant has not only provided little guidance as to what homologues may be capable of inducing interferon-γ production in cells generally, but the Applicant has not shown that even naturally occurring Il-18 from non-human sources is capable of inducing interferon-γ production in human cells, and therefore has provided little indication as to whether specific residues or sequences are required for the claimed function. Therefore, in view of the limited guidance provided by the Applicant, the breadth of the claims, and the lack of predictability in the art, the Applicant's arguments that they are enabled for the full scope of the rejected claims is not found persuasive, and the rejection is maintained.

10. **(Prior Rejection-Maintained)** Claims 18, 20, and 21-52 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims were rejected because the Application does not provide adequate support for claims to the genus of all homologues to the interferon-gamma inducing factor (IGIF) of SEQ ID NO: 6. The Applicant argues that the Applicant has disclosed two additional homologues of SEQ ID NO: 6 on pages 56 and 89. It is noted that each of these "homologues" comprises a sequence with an addition of one or two residues to the N terminal of the sequence. Thus, neither of these homologues comprises a substitution or deletion of residues within the protein sequence, which are the types of homologues of greatest concern in the present rejection (as indicated by the concern with changes to residues involved with the protein function). The Applicant further argues in traversal of the rejection that the state of the art should be considered in the rejection and is as described by the Watson reference indicated above. While the state of the art is relevant in as much as it relates to what those in the art would reasonably have understood to be in the Applicant's possession from the disclosure, the Examiner agrees that the state of the art may be relevant to some extent. It is not however the primary consideration, and as has been adequately discussed with respect to the enablement rejection above, does not indicate that those in the art would have reasonable understood that the Applicant was in possession of any homologue of SEQ ID NO: 6 with interferon-γ inducing activity.

As indicated in the prior action, the Applicant is attempting to claim a genus of inventions identified by the Applicant through a functional equivalence to SEQ ID NO: 6.

Although it was recognized by the Court of Appeals for the Federal Circuit that identifying a genus through functional language was permissible, the court indicated that such functional language must be accompanied by a "known or disclosed correlation between function and structure." Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. More recently, the Federal Circuit has also indicated that an inventor of "a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." Noelle v. Lederman (Fed Cir, No. 02-1187, 1/20/04). In the present case, the Applicant has provided no correlation between any particular structure and the functional language, and the art has indicated that there is unpredictability in the art concerning the making of homologues to a particular protein. In view of the above, the Applicant's traversal is not found persuasive, and the rejection is maintained.

Claim Rejections - 35 USC § 102

11. **(Prior Rejections- Withdrawn)** Claims 18, 20, 21, 24, 27, and 28 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,912,324, issued to Okamura et al. These claims read on homologues of SEQ ID NO: 6 having the properties of having a molecular weight of 18,500 ± 3,000 daltons, an isoelectric point of 4.9±1.0 on chromatofocusing, and a biological activity of inducing interferon-γ production. The Applicant argues that the peptide taught by Okamura does not meet the limitations of claim 18 as the protein contains additions or deletions outside of the N or C terminal fragments (identified as those of SEQ ID NO: 14 and 15

on page 6 of the specification). In view of these arguments, which are persuasive, the rejection is withdrawn.

12. **(Prior Rejection- Withdrawn)** Claims 18, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Joh et al., WO 98/10072. This rejection was traversed for reasons similar to those presented with respect to the Okamura reference above. In view of these arguments, which are persuasive, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

13. **(Prior Rejection- Withdrawn)** Claims 21-23, 25, 26, and 28-52 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 5,912,324, issued to Okamura et al., as applied against claims 18, 20, 21, 24, 27, and 28 above. The Applicant traverses this rejection on the grounds that this reference is commonly owned with the present application, and that the reference may therefore not be used as a reference under 35 U.S.C. 103(c). This argument is persuasive. The rejection is therefore withdrawn.

14. **(Prior Rejection- Withdrawn)** Claims 18, 20, 21, and 26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (J Immunol 155:785-795), in view of Okamura et al. (Nature 378:88-91). Applicant traversed this rejection for the same reasons as presented with respect to the anticipation rejection over the Okamura patent indicated above. In view of these arguments, which are persuasive, the rejection is withdrawn.

Conclusion

15. Claims 1, 2, and 4-9 are found allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 2/9/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600